Clomiphene Citrate in PCOS

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Gonadotrophins versus clomiphene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomiphene failure: A cost-effectiveness analysis

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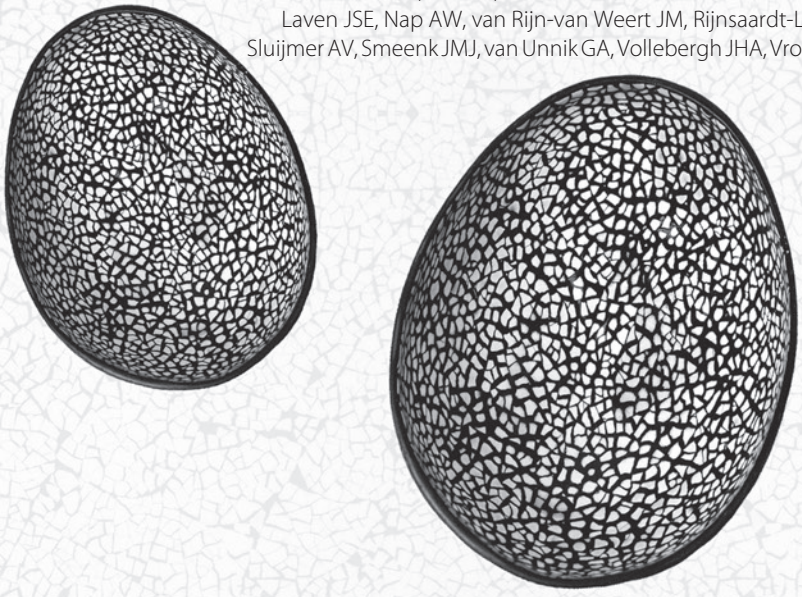

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ABSTRACT

Study question: Are six cycles of ovulation induction with gonadotrophins more cost-effective than six cycles of ovulation induction with clomiphene citrate (CC) with or without intra-uterine insemination (IUI) in normogonadotropic anovulatory women not pregnant after six ovulatory cycles with CC?

Summary answer: Both gonadotrophins and IUI are more expensive when compared with CC and intercourse, while gonadotrophins are more effective without any evidence of an increased effectiveness of IUI.

What is known already: In women with normogonadotropic anovulation who ovulate but do not conceive after six cycles with clomiphene citrate, medication is usually switched to gonadotrophins, with or without intrauterine insemination. Cost-effectiveness of these changes in policy is unknown.

Study design, size, duration: We performed an economic evaluation of ovulation induction with gonadotrophins compared with CC with or without IUI in a two-by-two factorial multicentre randomised controlled trial in normogonadotropic anovulatory women not pregnant after six ovulatory cycles with CC. Between December 2008 and December 2015 women were allocated to six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with CC plus IUI or six cycles with CC plus intercourse. The primary outcome was conception leading to a live birth achieved within 8 months of randomisation.

Participants/materials, setting, methods: We performed a cost-effectiveness analysis from a health care perspective. We calculated the direct medical costs of ovulation induction with gonadotrophins versus CC and of IUI versus intercourse in six subsequent cycles. We included costs of medication, cycle monitoring, interventions, and pregnancy leading to live birth. Recourse use was collected from the case report forms and unit costs were derived from various sources. We calculated incremental cost-effectiveness ratios (ICER) for gonadotrophins compared to CC and for IUI compared to intercourse. We used nonparametric bootstrap resampling to investigate the effect of uncertainty in our estimates. The analysis was performed according the intention-to-treat principle.

Main results and the role of chance: We allocated 666 women to gonadotrophins and IUI (n=166), gonadotrophins and intercourse (n=165), CC and IUI (n=163), or CC and intercourse (n=172). Mean direct medical costs per woman receiving

gonadotrophins or CC were €4495 versus €3007 (cost difference of €1475 (95% CI €1457 to €1493)). Live birth rates were 52% in women allocated to gonadotrophins and 41% in those allocated to CC (relative risk 1.24: 95% CI 1.05-1.46). The incremental cost-effectiveness ratio was €15 258 (95% CI €8721 to €63 654) per additional live birth with gonadotrophins.
Mean direct medical costs per woman allocated to IUI or intercourse were €4497 versus €3005 (cost difference of €1510 (95% CI €1492 to €1529)). Live birth rates were 49% in women allocated to IUI and 43% in those allocated to intercourse (relative risk 1.14: 95% CI 0.97-1.35). The incremental cost-effectiveness ratio was €24 361 (95% CI €-11 290 to €85 172) per additional live birth with IUI.

Limitations, reasons for caution: We allowed participating hospitals to use their local protocols for ovulation induction and IUI, which may have led to variation in costs, but which increases generalisability. We did not implement indirect costs generated by transportation or productivity loss. We did not evaluate letrozole, which is potentially more effective than CC.

Wider implications of the findings: Because gonadotrophins are more effective, but more expensive than CC, the use of gonadotrophins in women with normogonadotropic anovulation who have not conceived after six ovulatory CC cycles depends on society's willingness to pay for an additional child. In view of the uncertainty around the cost-effectiveness estimate of IUI, data are not sufficient to make recommendations on the use of IUI in these women.

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Trial registration: NTR1449

INTRODUCTION

In women with normogonadotropic anovulation who wish to conceive, clomiphene citrate (CC) has long been used as first line treatment for ovulation induction.[1-4] Women not conceiving after six ovulatory cycles are defined as having CC failure.[5] In daily practice, these women often switch to ovulation induction with gonadotrophins and intrauterine insemination (IUI) is often initiated instead of relying on regular intercourse.[2]

The evidence for such a policy change has long been lacking. We recently reported the results of the Modified Ovulation Induction (M-ovin) study, a two-by-two factorial multicentre randomised controlled trial (RCT) comparing ovulation induction with gonadotrophins to CC with or without IUI in normogonadotropic anovulatory women with CC failure.[6] In that study, we randomly assigned women to either six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with CC plus IUI or six cycles with CC plus intercourse. The primary outcome was a live birth achieved within 8 months of randomisation. We made two comparisons, one in which gonadotrophins were compared with CC and one in which IUI was compared with intercourse. This trial showed that a switch of treatment to gonadotrophins led to an absolute increase in live birth of 10% over treatment with CC. IUI did not lead to an increase in live births compared with intercourse.

In view of limited health care resources, costs are also important in deciding which treatment should be advised to patients. In contrast to CC, which is relatively cheap due to the low price of the tablets and limited monitoring requirements, ovulation induction with gonadotrophins is expensive due to the price of medication and the need for strict ultrasound monitoring.[7-10] Knowledge on the relative cost and effectiveness of these interventions with or without IUI is lacking. The aim of this study was to provide an economic evaluation of ovulation induction with gonadotrophins compared to CC with or without IUI in women with CC failure.

MATERIALS AND METHODS

Study design

This economic evaluation was performed alongside the M-ovin study, a two-by-two factorial RCT in 48 Dutch hospitals that compared ovulation induction with gonadotrophins with CC with or without IUI in normogonadotropic anovulatory women with CC failure. Details about the study design, sample size calculation, study procedures and outcomes have been described previously.[11,6] Ethical approval was obtained by the Medical Ethical Committee of the Medical Spectrum Twente Enschede (Netherlands) and from the Central Committee on Research involving Human Subjects (CCMO, Netherlands). The board of directors of each of the participating centres approved local execution of the study.

In short, sub-fertile women of at least 18 years of age with normogonadotropic anovulation who had been ovulatory for six cycles on CC, but who had not conceived, were eligible for the trial. Couples with male subfertility and double sided tubal pathology could not participate. Women were randomly assigned using a central password protected internet-based randomisation programme. The randomisation list had been prepared by an independent statistician with a variable block size and a maximum block size of 8. There was no masking. Consenting women were randomly allocated to any of four treatments on a 1:1:1:1 basis, i.e. six cycles of gonadotrophins plus IUI, six cycles of gonadotrophins plus intercourse, six cycles of CC plus IUI or six cycles of CC plus intercourse. We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation induction with gonadotrophins versus continuing CC and IUI versus intercourse.

Ovulation induction, cycle monitoring, semen preparation and insemination were performed according to local hospital protocols. The starting dose of gonadotrophins was 50 or 75 IU daily and participating clinics used either urinary or recombinant gonadotrophins depending on their local protocol. Follicular growth was monitored by transvaginal ultrasound. We used 5000 IU of human chorionic gonadotrophin (hCG) to trigger ovulation. The dosage of CC was a minimum of 50 mg to a maximum of 150 mg daily, for five days. If ovulation did not occur, the dosage was increased with steps of 50 mg with a maximum of 150 mg daily in the next cycles. Women undergoing ovulation induction with CC plus IUI underwent monitoring by ultrasound, women undergoing CC plus intercourse were usually monitored by basal body temperature curve, mid luteal progesterone measurement or urinary luteal hormone surge depending on the local protocol. In the case of IUI, a single insemination per cycle was performed.

The primary outcome measure was conception leading to a live birth within eight months after randomisation. A live birth was defined as any baby that was born alive after a gestational age beyond 24 weeks. Secondary outcomes included multiple pregnancy rate, ongoing pregnancy rate, miscarriage, and ectopic pregnancy.

Economic evaluation

The economic evaluation was performed as a cost-effectiveness analysis from a health care perspective, thus focusing on direct medical costs during treatment.

Resource use

Data on resource use were collected from the individual case report forms of the RCT. For each woman, we registered the medication, cycle monitoring (number of ultrasounds), and interventions (cycles with IUI, cycles with IVF) they received within six subsequent cycles or until a live birth occurred within a time horizon of 8 months. If women changed their

treatment to IVF/ICSI, resource use was estimated on the basis of previously published data on resource costs for IVF/ICSI.[12] Within the M-ovin study, 21 women switched to treatment with IVF or ICSI during their study period i.e. before finishing their allocated treatment (8 women who were allocated to FSH+IUI, 4 women who were allocated to FSH, 7 women who were allocated to CC+IUI, 3 women who were allocated to CC). Because of the intention to treat principle that we have used, the pregnancies resulting from treatment with IVF/ICSI were included in the main analysis of our RCT.

Unit costs

Direct unit costs included the costs of medication, cycle monitoring, interventions, and the costs of pregnancy leading to live birth. The costs for medication and the unit costs of cycle monitoring and interventions were obtained from the costs as retrieved by an expert panel on cost-effectiveness from the Dutch Consortium for Research in Women's Health. The expert panel, consisting of gynecologists, economists and a methodologist, collected the actual total medical costs per cost unit from resources that are being used in fertility studies within our Consortium from two university hospitals and one general hospital. For our final calculation we used the average costs of the three Dutch hospitals.

We derived costs for pregnancy and delivery from a cost analysis of singleton versus twin pregnancies, in which the costs for a singleton and twin pregnancies up until 6 weeks after delivery was described.[13] The costs of a miscarriage with or without curettage, ectopic pregnancy and stillbirth were obtained from the pricelist of one general hospital. All costs were expressed in 2017 euros (€) and corrected for inflation or deflation whenever necessary using the consumer pricing index.[14]

Statistical analysis

For each of the four treatments we calculated the mean costs and effectiveness on the basis of the intention-to-treat principle. For effectiveness we calculated absolute risks, relative risks and corresponding 95% boundaries. Costs were calculated by multiplying the quantity of resource use and unit costs. For each treatment we calculated the mean cost per woman. For costs we calculated mean cost differences and 95% boundaries as estimated on the basis of bootstrapping by taking 1000 random samples. Costs were combined with effectiveness by calculating Incremental Cost-Effectiveness Ratios (ICER) for gonadotrophins compared with CC and for IUI compared with intercourse. The ICER was defined as the ratio between the differences in costs and the differences in effects between two interventions. We used a non-parametric bootstrap resampling to investigate the effect of uncertainty in our estimates. The uncertainty was visualized by plotting a cost-effectiveness plane. CC and intercourse were the reference strategies (in the origin of the cost-effectiveness plane).

We drew a cost-effectiveness acceptability curve, expressing the probability that a strategy will be cost-effective at a specific willingness-to-pay for an additional child, given the uncertainty. The range was from 0 to 135 000 euros.
In view of the factorial design, we investigated the interaction between IUI and ovulation induction with costs. We first evaluated if factors have a multiplicative effect and used a general linear model in transformed cost data.

Per protocol and sensitivity analyses

We did a per-protocol analysis in which we included women who were actually treated according to the predefined protocol.[11] We performed four one way sensitivity analyses to explore the impact of key factors in the cost-effectiveness analyses. In the first analysis we excluded IVF cycles (Model 1), in the second we used ongoing pregnancy as main measure of effectiveness (Model 2), in the third we calculated with unit costs used in the United Kingdom which were collected from a NHS hospital (Model 3), in the fourth we assumed that all CC-cycles were monitored by ultrasound (Model 4) and in the fifth that none of the CC-cycles were monitored by ultrasound (Model 5). All statistical analyses were performed using SPSS (version 23.0; IBM Corp., USA) and Microsoft Excel (version 2016) for the bootstrapping.

RESULTS

Study population and effectiveness outcomes

Between December 2008 and December 2015, we randomised 666 women: 166 women were allocated to ovulation induction with gonadotrophins combined with IUI, 165 to ovulation induction with gonadotrophins, 163 to ovulation induction with CC combined with IUI, and 172 to continued ovulation induction with CC. Five women were excluded since they had been erroneously randomised. The baseline characteristics of the participating women can be found in appendix 1.
Effectiveness outcomes are summarized in Table I. Live birth rates were 52% after gonadotrophins versus 41% after CC, RR 1.24 (95% CI 1.05-1.46); absolute difference 10.2% (95% CI 2.4–17.9). Live birth rates were 49% after IUI versus 43% after intercourse, RR 1.14 (95% CI 0.97-1.35); absolute difference 6.1% (95% CI –1.71 to 13.8). There was no interaction between CC or gonadotrophins and presence of IUI on live birth (p=0.0124). Multiple pregnancy rates were low and did not differ significantly for both comparisons. The mean time to pregnancy was 0.5 months shorter after ovulation induction with gonadotrophins compared to ovulation induction with CC (log rank p=0.028) whereas the mean time to pregnancy was the same when comparing IUI with intercourse (log rank p=0.27).

Table I. Primary and secondary outcomes

	Gonado-trophins + IUI n = 164	Gonado-trophins n = 163	CC + IUI n = 163	CC n = 171	Gonado-trophins vs CC Rate difference RR (95% CI)	IUI vs intercourse Rate difference RR (95% CI)
Live birth	89 (54.3)	78 (47.9)	72 (44.2)	66 (38.6)	1.24 (1.05-1.46)	1.14 (0.97-1.35)
Ongoing pregnancy	90 (54.9)	80 (49.1)	72 (44.2)	66 (38.6)	1.26 (1.07-1.48)	1.14 (0.97-1.34)
Multiple pregnancy	4 (2.4)	3 (1.8)	7 (4.3)	1 (0.6)	0.89 (0.33-2.40)	2.8 (0.90-8.70)
Miscarriages*	15 (9.1)	9 (5.5)	8 (4.9)	3 (1.8)	-	-
Ectopic pregnancy*	1 (0.6)	1 (0.6)	3 (1.8)	1 (0.6)	-	-
Stillbirth*	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	-	-

Data are n (%) unless otherwise stated.
All multiple pregnancies were twin pregnancies and live births.
* Secondary outcomes.

Economic evaluation

Resource use and unit costs

The mean resource use per woman is summarized in Table II. The number of ultrasounds were higher in the women who received gonadotrophins, which resulted in more hospital visits. Women who received CC were also monitored with basal body temperature curve, mid luteal progesterone measurement or urinary LH surge, which resulted in less monitory ultrasounds and therefore less hospital visits compared to gonadotrophins. Women allocated to gonadotrophins with or without IUI and CC plus IUI received a HCG-trigger. No HCG-trigger was given to the women allocated to CC plus intercourse. Unit costs are listed in Table III.

Table II. Resource use per woman*

	Gonadotrophins + IUI	Gonadotrophins	CC + IUI	CC
Cycle monitoring/Intervention				
- Ultrasound (N)	15.87 (10.53)	16.67 (10.66)	12.69 (7.72)	8.31 (5.98)
- IUI (N)	3.22 (2.26)	0.15 (0.71)	3.57 (2.30)	0.12 (0.55)
- IVF (N)	0.04 (0.20)	0.02 (0.16)	0.06 (0.36)	0.03 (0.25)
Medication				
- CC (50mg)	0.18 (1.27)	0.48 (2.91)	28.37 (22.74)	26.16 (21.02)
- FSH (75 IU)	36.00 (32.76)	39.94 (37.29)	2.87 (12.35)	4.84 (14.15)
- HCG (5000 IU)	3.27 (2.32)	3.42 (2.27)	3.69 (2.32)	0.49 (1.26)

* Data are mean (SD).

Table III. Unit costs

Cost item	Unit	Unit costs (Euros)	Reference
Cycle monitoring/Interventions			
- Ultrasound	1	62.50	Dutch Consortium*
- IUI	1	320.54	Dutch Consortium*
- IVF	1	1365.84	Dutch Consortium*
Medication			
- CC	50mg	0.53	Dutch Consortium*
- FSH	75 IU	24.75	Dutch Consortium*
- HCG	5000 IU	5.83	Dutch Consortium*
Pregnancy and delivery			
- Singleton	1	3107.00	Lukassen *et al* 2004
- Twin	1	16 419.00	Lukassen *et al* 2004
- Miscarriage	1	1494.76	One general hospital
- Ectopic pregnancy	1	4295.65	One general hospital
- Stillbirth	1	3107.00	One general hospital

Unit costs are based on Dutch price levels in 2017.
* Costs are derived from the expert panel Dutch Consortium for Research in Women's Health.

Costs

The mean costs per woman eight months after randomisation were €4984 for gonadotrophins plus IUI, €4003 for gonadotrophins plus intercourse, €4006 for CC plus IUI for €2045 with CC plus intercourse (Fig 1A).

For the comparison gonadotrophins versus CC we found mean costs per woman of €4495 with gonadotrophins and €3007 with CC (cost difference was €1475 (95% CI €1457 to €1493)) (Fig 1B). For the comparison IUI versus intercourse we found mean costs per woman of €4497 with IUI and €3005 with intercourse (cost difference was €1510 (95% CI €1492 to €1529)) (Fig 1C).

Cost-effectiveness

The ICER for ovulation induction with gonadotrophins compared with ovulation induction with CC was €15 258 (95% CI €8721 to €63 654) reflecting the additional costs necessary to achieve one additional live birth in women treated with gonadotrophins compared with CC. The majority of the bootstrap samples were located in the northeastern quadrant, reflecting higher costs with higher effectiveness for gonadotrophins versus CC (Fig. 2).

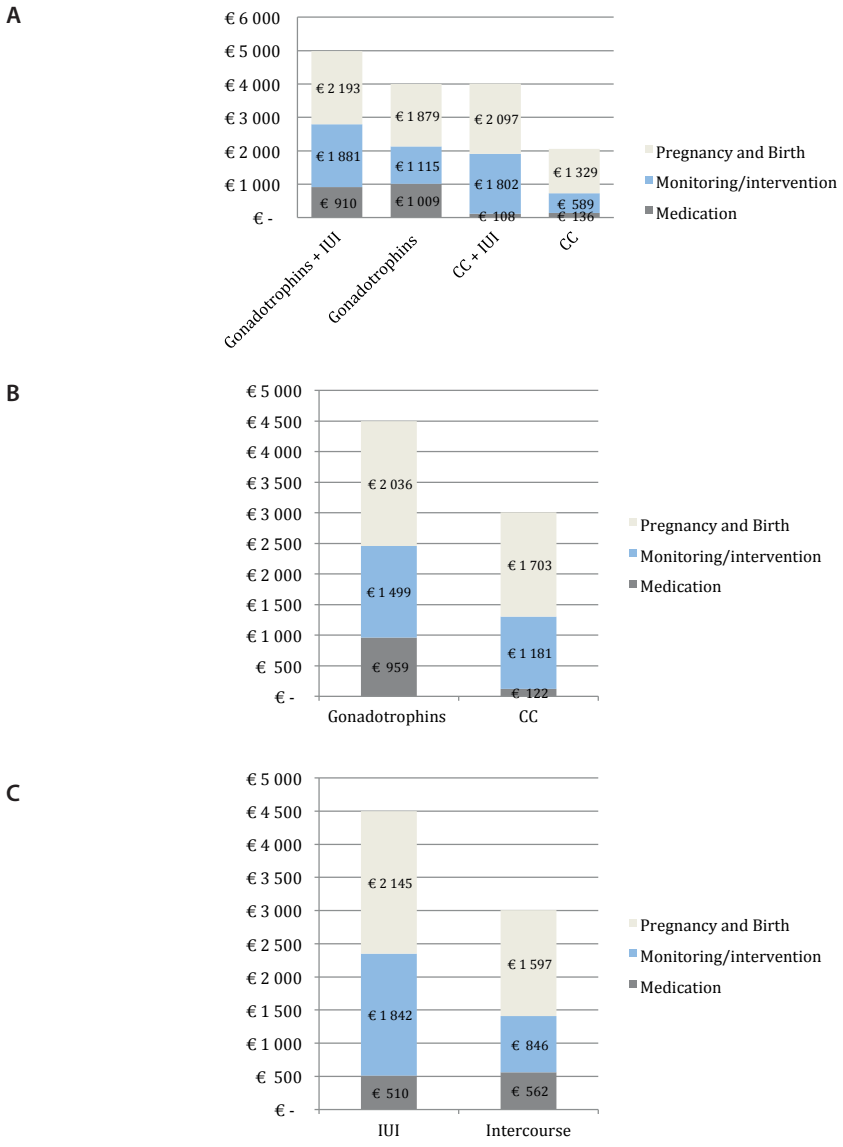


Figure 1. Mean costs per woman

A. Mean costs per woman for gonadotrophins plus IUI, gonadotrophins plus intercourse, CC plus IUI and CC plus intercourse split into the mean costs of medication, cycle monitoring/interventions (number of ultrasounds, cycles with IUI, use of IVF) and pregnancy leading to live birth. All costs are expressed in euros.

B. Mean costs per woman for the comparison gonadotrophins versus CC split into the mean costs of medication, cycle monitoring/interventions (number of ultrasounds, cycles with IUI, use of IVF) and pregnancy leading to live birth. All costs are expressed in euros.

C. Mean costs per woman for the comparison IUI versus intercourse split into the mean costs of medication, cycle monitoring/interventions (number of ultrasounds, cycles with IUI, use of IVF) and pregnancy leading to live birth. All costs are expressed in euros.

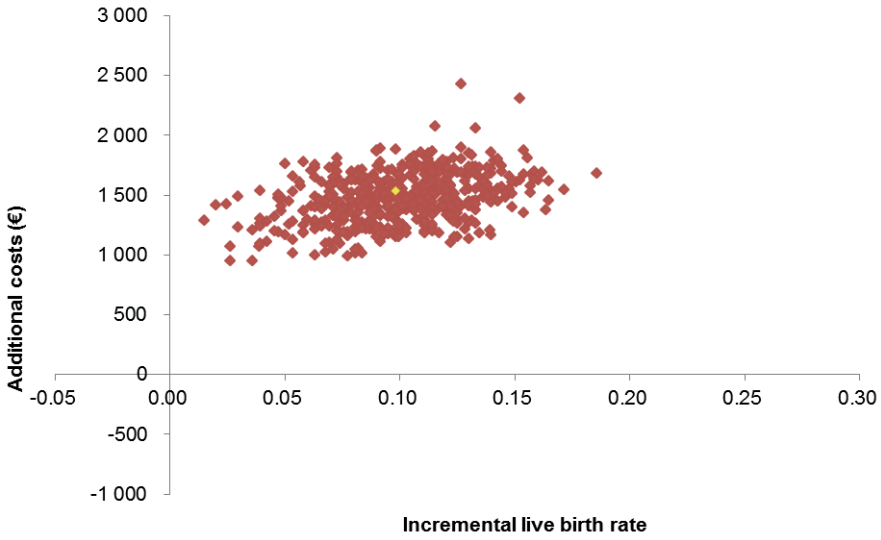


Figure 2. Cost-effectiveness plane gonadotrophins compared with CC

Cost-effectiveness plane: gonadotrophins versus CC. Each point in the cost-effectiveness plane represents the uncertainty of the additional costs and effect of gonadotrophins compared with CC after nonparametric bootstrap resampling (1000 random samples). The light grey dot in the middle represents the cost-effectiveness rate.

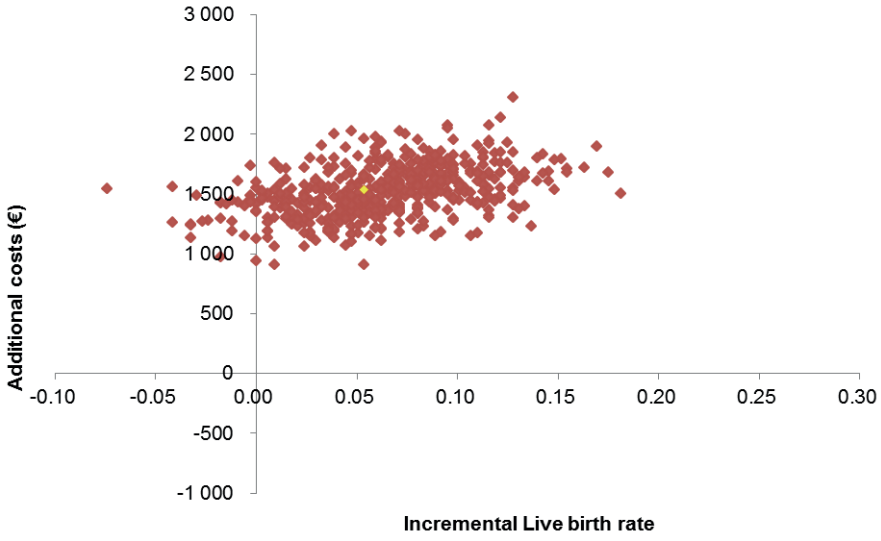


Figure 3. Cost-effectiveness plane IUI compared with intercourse

Cost-effectiveness plane: IUI versus intercourse. Each point in the cost-effectiveness plane represents the uncertainty of the additional costs and effect of IUI compared with intercourse after nonparametric bootstrap resampling (1000 random samples). The light grey dot in the middle represents the cost-effectiveness rate.

The ICER for IUI compared with intercourse was €24 361 (95% CI €-11 290 to €85 172) reflecting the additional costs necessary to achieve one additional live birth in the IUI group, compared with intercourse. The majority of the bootstrap samples were located in the north eastern quadrant (95%), reflecting higher costs with comparable effectiveness for IUI versus intercourse (Fig. 3).
For both comparisons we drew a cost-effectiveness acceptability curve (appendix 2). For a willingness-to-pay of €15 000 for an additional live birth, there is 51% chance that gonadotrophins is cost-effective compared with CC and this was 96% for a willingness to pay of €30 000. For a willingness-to-pay of €15 000 for an additional live birth, there is 15% chance that IUI is cost-effective compared with intercourse and this was 61% for a willingness to pay of €30 000.
Costs increased as more and more complex interventions were ordered, i.e. from CC, gonadotrophins, CC plus IUI, to gonadotrophins plus IUI. This implies costs were additive. The general linear model analysis did not indicate presence of interaction between IUI and ovulation induction on costs (p=0.62).

Per protocol and sensitivity analyses

Of the 666 women, 566 women were treated according to protocol and were included in the analysis. We noted more livebirths after gonadotrophins compared with CC, 125 (46%) of 274 women after gonadotrophins versus 95 (33%) of 292 women after CC (RR 1.39 (95% CI 1.10 – 1.57) absolute difference 13%). We found mean costs per woman of €4550 with gonadotrophins and €2596 with CC (cost difference was €2056 (95% CI €2040 - €2072)). The ICER for ovulation induction with gonadotrophins compared with ovulation induction with CC was €15 582 (95% CI €10 013 – €37 323) which is higher compared to the intention-to-treat ICER.
Addition of IUI did not significantly increase livebirths compared with intercourse: 118 (42%) of 281 women had a livebirth after IUI versus 102 (36%) of 285 women after intercourse (RR 1.14 (95% CI 0.96–1.36) absolute difference 6%). We found mean costs per woman of €4282 with IUI and €2578 with intercourse. The cost difference was €1586 (95% CI €1568 - €1604). The ICER for IUI compared with intercourse was €25 628 (95% CI €-11 870 – €72 340) which is higher compared to the intention-to-treat ICER.
For the comparison of gonadotrophins versus CC the results of the sensitivity analyses are shown in Table IV a. If we excluded IVF cycles (Model 1), the ICER was €15 426. When ongoing pregnancy was the main measure of effectiveness (Model 2) the ICER was €11 157. Calculating with unit costs of the United Kingdom (Model 3) resulted in a ICER was £19 744. If all CC-cycles were 100% monitored by ultrasound (Model 4) the ICER would lower to €13 460 and if none of the CC-cycles were monitored by ultrasound (Model 5) the ICER would increase to €17 222.

For the comparison of IUI versus intercourse the results of the sensitivity analyses are shown in Table IV b. If we excluded IVF cycles (Model 1), the ICER was €23 786. When ongoing pregnancy was the main measure of effectiveness (Model 2) the ICER was €17 531. Calculating with unit costs of the United Kingdom (Model 3) resulted in a ICER of £34 420.

Table IV. One way sensitivity analyses in Euro

Model	Description	Mean cost gonadotrophins (SD)	Mean cost CC (SD)	Difference (95% CI#)	ICER (95% CI#)
0	Base case	4536 (2501)	2996 (2735)	1475 (1457 to 1493)	15 258 (8721 to 63 654)
1	Excluded IVF	4504 (4504)	3020 (2791)	1507 (1490 to 1525)	15 426 (8852 to 64 210)
2	Endpoint ongoing pregnancy	2495 (1858)	1356 (1283)	1190 (1180 to 1201)	11 157 (5567 to 43 736)
3	Costs UK*	5410 (3033)	3429 (2824)	1918 (1898 to 1938)	19 744 (11 036 to 86 114)
4	All CC cycles monitored with ultrasound	4609 (2699)	3195 (2586)	1311 (1293 to 1329)	13 460 (7592 to 55 704)
5	CC cycles not monitored with ultrasound	4496 (3109)	2662 (2830)	1677 (1659 to 1695)	17 222 (9923 to 72 383)

A. Gonadotrophins compared with CC.
Model 0: Base case, live birth as effectiveness outcome, Model 1: Excluded all IVF cycles; effectiveness outcome live birth remained fixed, Model 2: The costs of pregnancy and birth were excluded (costs for miscarriage and ectopic are still included), effectiveness outcome was changed to ongoing pregnancy, Model 3: Effectiveness outcome live birth remained fixed, and costs from a UK (NHS) were used as input, Model 4: All CC cycles monitored with ultrasound; effectiveness outcome live birth remained fixed, Model 5: None of the CC cycles are monitored with ultrasound but with basal body temperature curve, mid luteal progesterone measurement or urinary LH surge.
#Non-parametric confidence interval based on 1000 bootstrap replications.
* Costs UK are in pounds.

DISCUSSION

We performed an economic evaluation alongside a two-by-two factorial multicentre RCT comparing ovulation induction with gonadotrophins with CC, and IUI with intercourse in women with normogonadotropic anovulation and CC failure. Women allocated to gonadotrophins had significantly more live births than those allocated to CC, but at higher costs. These higher costs were generated by more ultrasound monitoring and higher costs of medication in the gonadotrophin group. The additional cost necessary to achieve one additional live birth was €15,258 (95% CI €8721 to €63,654).

Women allocated to IUI did not have significantly more live births than those allocated to intercourse. The costs were significantly higher for women assigned to IUI compared with intercourse. The additional cost necessary to achieve one additional live birth was €24,361

(95% CI €-11.290 to €85.172). The wide confidence interval, crossing unity, implicates a large degree of uncertainty around the cost-effectiveness.

The present study has several strengths. First, we designed the study to assess live birth rates which is the most important outcome from the patient's perspective. Second, this economic evaluation was based on a randomised study with prospective registration of resource use. We incorporated all interventions and associated costs that took place in eight months, closely reflecting daily practice. Third, by performing several sensitivity analyses, we showed that our outcomes were robust making the results applicable to other hospitals. Finally, in the per-protocol analysis and the four sensitivity analyses CC and intercourse remained less costly, indicating that our results are robust when varying several treatment details.

A weakness of our study is that we allowed participating hospitals to use their local protocols for ovulation induction and IUI, which resulted in heterogeneous data on cycle monitoring and that we did not take into account indirect costs generated by transportation or productivity loss.

Our finding that continuing CC is less costly than switching to gonadotrophins matches the results of a cost-effectiveness study in women with PCOS using fictional treatment scenarios.[9] In that study, continuing CC for another six cycles followed by six or twelve cycles with gonadotrophins, followed by IVF was more cost-effective than a direct switch to gonadotrophins followed by IVF. The cost-effectiveness of IUI was not included in that study.

Several recent studies have shown that first line treatment with the aromatase inhibitor Letrozole is associated with higher live birth rates than with CC as was summarized in a network meta-analysis.[15] Letrozole tablets are only slightly more expensive than CC tablets.[16] A cost-effectiveness analysis comparing Letrozole with gonadotrophins in women with CC failure could result in a smaller cost difference than with gonadotrophins, but this needs to demonstrated before conclusions are drawn.

Since our cost-effectiveness analysis used a health care perspective, we focused on direct medical costs during treatment. From a societal perspective, indirect costs generated by transportation or productivity loss can also contribute to the costs of the ovulation induction treatments. Treatment with gonadotrophins plus IUI leads to more visits to the clinic in view of cycle monitoring and interventions and would thus result in more indirect costs. As a consequence, including societal costs would enlarge the cost difference between gonadotrophins and CC, and IUI and intercourse. On the other hand, due to the higher live birth rates after gonadotrophins, fewer cycles would need to be performed. Thus, over the treatment period of eight months, this potential difference in costs may disappear.

The unit costs of the interventions vary between countries. Country-specific prices and assumptions need to be considered before generalizing these results to other countries. When using prices from a NHS teaching hospital in the United Kingdom, we found that

the mean costs were higher for both gonadotrophins and IUI, leading to more costs per additional live birth for gonadotrophins compared with CC and for IUI compared with intercourse. In countries where the unit costs are higher, such as the United States, it is likely that gonadotrophins and IUI will be even more expensive.

Cost-effectiveness of interventions have to be known, but are -in themselves- not decisive in finalizing the optimal treatment policy. Decisive is the 'willingness to pay' i.e. the monetary value that society is willing to pay for higher live birth rates, but the problem is that there is no consensus on the level of costs per extra live birth that is acceptable. The NICE Fertility Guideline suggests a threshold of £30.000 per quality adjusted life year (QALY), but also highlights that QALYs cannot be derived from live births arising from assisted reproduction as QALYs are intended to capture improvements in health among patients and not in creating life. Patient preference studies in subfertile women reveal that couples are willing to pay €100-€500 extra to increase pregnancy rates by a few percent.[17,18]

In conclusion, in women with normogonadotropic anovulation who have not conceived after six ovulatory CC cycles, gonadotrophins are more effective, but generate higher costs compared to CC. In countries where ovulation induction regimens are reimbursed, policy makers and health care professionals may use our results in their guidelines. Importantly, apart from the costs, couples must be counseled that CC is known to cause more side-effects than gonadotrophins, whereas gonadotrophins require daily injections combined with ultrasound monitoring of follicular development.[10]

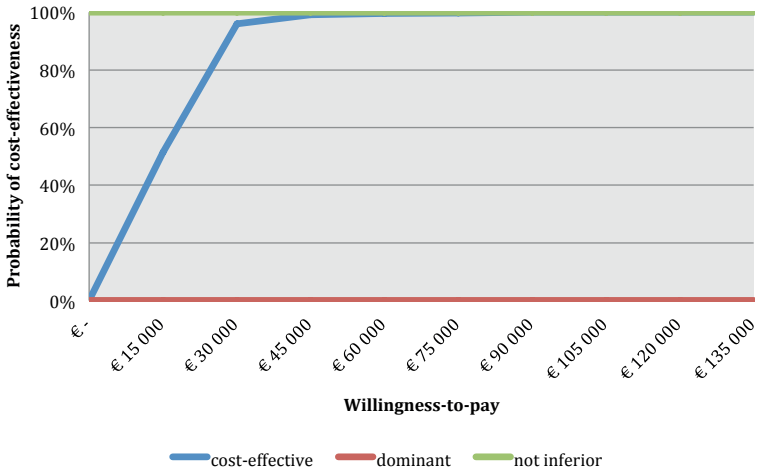
In view of the uncertainty around the cost-effectiveness estimate of IUI, we cannot make recommendations on the use of IUI in these women and more data are needed.

Appendix 1. Baseline characteristics of the participating couples

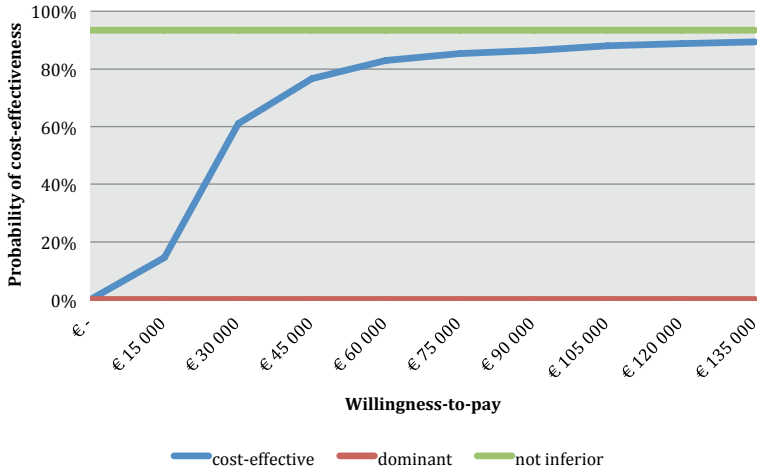
	Gonadotrophins + IUI n = 164	**Gonadotrophins + intercourse n = 163**	**CC + IUI n = 163**	**CC + intercourse n = 171**
Age of women (years)	29·5 ± 3·7	29·9 ± 3·7	30·0 ± 3·6	29·9 ± 4·0
Ethnicity				
White	131 (85%)	134 (88%)	133 (86%)	141 (89%)
Non-white	24 (15%)	18 (12%)	21 (14%)	18 (11%)
BMI (kg/m^2)*	25·4 ± 5·1	25·6 ± 5·6	25·0 ± 4·9	25·4 ± 5·0
BMI >25.0 kg/m^2	76 (46%)	81 (49%)	64 (39%)	81 (47%)
Current smoker	29 (18%)	20 (12%)	22 (13%)	22 (13%)
Diabetes	1	1	3	2
Previous livebirth	32 (20%)	35 (21%)	36 (22%)	34 (20%)
Duration of subfertility (months)	26·3 ± 14·9	24·5 ± 12·5	24·5 ± 15·5	25·9 ± 19·0
Cycle pattern prior to treatment #				
Amenorrhea	124 (76%)	125 (77%)	115 (71%)	120 (70%)
Oligomenorrhea	21 (13%)	25 (15%)	27 (16%)	32 (19%)
Unknown	19 (11%)	13 (8%)	21 (13%)	19 (11%)
Median TMC *10^6	52 (20-106)	43 (16-113)	53 (15-132)	38 (16-99)
Polycystic ovaries on ultrasound ##	110 (67%)	103 (63%)	109 (67%)	117 (68%)
Mean serum biochemical values				
FSH (IU/L)	5·7 ± 2·1	5·7 ± 1·7	6·2 ± 2·2	6·0 ± 2·2
LH (IU/L)	9·7 ± 7·4	10·6 ± 7·8	10·6 ± 7·6	10·9 ± 10·8
Estrogen (pmol/L)	255 ± 295	239 ± 217	201 ± 159	271 ± 460
Total testosterone (nmol/L)	1·6 ± 1·7	1·6 ± 2·0	1·8 ± 2·2	1·8 ± 1·8

Data are mean (SD), n (%) or median (IQR). BMI = body-mass index. TMC = total motile sperm count. FSH = follicle stimulating hormone. LH = luteinizing hormone. CC = clomiphene citrate. IUI = intrauterine insemination.
*BMI was missing for 24 women; data were imputed by using multiple imputation.
Amenorrhea: absence of menstrual bleeding for >6 months. Oligomenorrhea: irregular menstrual bleedings with intervals of >35 days but ≤6 months
Defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter

Appendix 2. Cost-effectiveness acceptability curves



This cost-effectiveness acceptability curve shows the probability that FSH is cost-effective compared with CC, given the observed data, for a range of values of the willingness to pay for an additional live birth.



This cost-effectiveness acceptability curve shows the probability that IUI is cost-effective compared with intercourse, given the observed data, for a range of values of the willingness to pay for an additional live birth.

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